CLAIMS

What is claimed is:

1. A truncated sTNFR having the following formula:

R_1-[Cys^{19}-Cys^{103}]-R_2

wherein [Cys^{19}-Cys^{103}] represents residues 19 through 103 of sTNFR-I, the amino acid residue numbering scheme of which is provided in Figure 1 (SEQ ID NO:2) to facilitate the comparison;

wherein R_1 represents a methionylated or nonmethionylated amine group of Cys^{19} or of amino-terminus amino acid residue(s) selected from the group:

C
IC
SIC
NSIC (SEQ ID NO:15)
NNSIC (SEQ ID NO:16)
QNNSIC (SEQ ID NO:17)
PQNNSIC (SEQ ID NO:18)
HPQNNSIC (SEQ ID NO:19)
IHPQNNSIC (SEQ ID NO:20)
YIHPQNNSIC (SEQ ID NO:21)
KYIHPQNNSIC (SEQ ID NO:22)
GKYIHPQNNSIC (SEQ ID NO:23)
QGKYIHPQNNSIC (SEQ ID NO:24)
PQGKYIHPQNNSIC (SEQ ID NO:25)
CPQGKYIHPQNNSIC (SEQ ID NO:26)
VCPQGKYIHPQNNSIC (SEQ ID NO:27)
SVCPQGKYIHPQNNSIC (SEQ ID NO:28)
DSVCPQGKYIHPQNNSIC (SEQ ID NO:29);

and wherein R_2 represents a carboxy group of Cys^{103} or of carboxy-terminal amino acid residues selected from the group:

F
FC
FCC
FCCS (SEQ ID NO:30)
FCCSL (SEQ ID NO:31)
FCCSLC (SEQ ID NO:32)
FCCSLCL (SEQ ID NO:33);

and variants and derivatives thereof, provided however, when R_1 represents a methionylated or nonmethionylated amine group of amino acid sequence VCPQGKYIHPQNNSIC or an N-terminal truncation thereof of from 1 to 15 residues, then R_1-[Cys^{19}-Cys^{103}]-R_2 is not an addition variant having the formula R_1-[Cys^{19}-Cys^{103}]-FCCSLCL-R_3, wherein R_3 represents a carboxyl group of amino acid residues Asn^{111}-Asn^{161} of Figure 1 or a carboxy-terminal truncation of Asn^{111}-Asn^{161} of Figure 1.

2. The tumor necrosis binding protein according to Claim 1, selected from the group consisting of sTNFR-I 2.6D/C105, sTNFR-I 2.6D/C106, sTNFR-I 2.6D/N105, sTNFR-I 2.3D/d8, sTNFR-I 2.3D/d18 and sTNFR-I 2.3D/d15 or a variant or derivative thereof.

3. A truncated sTNFR having the following formula:

R_4-[Cys^{32}-Cys^{115}]-R_5

wherein [Cys^{32}-Cys^{115}] represents residues Cys^{32} through Cys^{115} of mature, full-length 40kDa TNF inhibitor, the amino acid residue numbering scheme of which is provided in Figure 8 (SEQ ID NO:35) to facilitate the comparison;

wherein R_4 represents a methionylated or nonmethionylated amine group of Cys^{32} or of amino-terminus amino acid residue(s) selected from the group:

C
MC
QMC
AQMC (SEQ ID NO:36)
TAQMC (SEQ ID NO:37)
QTAQMC (SEQ ID NO:38)
DQTAQMC (SEQ ID NO:39)
YDQTAQMC (SEQ ID NO:40)
YYDQTAQMC (SEQ ID NO:41)
EYYDQTAQMC (SEQ ID NO:42)
REYYDQTAQMC (SEQ ID NO:43)
LREYYDQTAQMC (SEQ ID NO:44)
RLREYYDQTAQMC (SEQ ID NO:45)
CRLREYYDQTAQMC (SEQ ID NO:46)
TCRLREYYDQTAQMC (SEQ ID NO:47)
STCRLREYYDQTAQMC (SEQ ID NO:48)
GSTCRLREYYDQTAQMC (SEQ ID NO:49)
PGSTCRLREYYDQTAQMC (SEQ ID NO:50)
EPGSTCRLREYYDQTAQMC (SEQ ID NO:51)
PEPGSTCRLREYYDQTAQMC (SEQ ID NO:52)
APEPGSTCRLREYYDQTAQMC (SEQ ID NO:53)
YAPEPGSTCRLREYYDQTAQMC (SEQ ID NO:54)
PYAPEPGSTCRLREYYDQTAQMC (SEQ ID NO:55)
TPYAPEPGSTCRLREYYDQTAQMC (SEQ ID NO:56)
FTPYAPEPGSTCRLREYYDQTAQMC (SEQ ID NO:57)
AFTPYAPEPGSTCRLREYYDQTAQMC (SEQ ID NO:58)
VAFTPYAPEPGSTCRLREYYDQTAQMC (SEQ ID NO:59)
QVAFTPYAPEPGSTCRLREYYDQTAQMC (SEQ ID NO:60)
AQVAFTPYAPEPGSTCRLREYYDQTAQMC (SEQ ID NO:61)
PAQVAFTPYAPEPGSTCRLREYYDQTAQMC (SEQ ID NO:62)
LPAQVAFTPYAPEPGSTCRLREYYDQTAQMC (SEQ ID NO:63);

and wherein R_5 represents a carboxy group of Cys^{115} or of carboxy-terminal amino acid residues selected from the group:

A
AP
APL
APLR (SEQ ID NO:64)
APLRK (SEQ ID NO:65)
APLRKC (SEQ ID NO:66)
APLRKCR (SEQ ID NO:67)

and variants thereof, provided however, when R_4 represents a methionylated or nonmethionylated amine group of amino acid sequence TCRLREYYDQTAQMC or an N-terminal truncation thereof of from 1 to 15 residues, then R_4-[Cys^{32}-Cys^{115}]-R_5 is not an addition variant having the formula R_4-[Cys^{32}-Cys^{115}]-APLRKCR-R_6, wherein R_6 represents a carboxyl group of amino acid residues Pro^{123}-Thr^{179} of Figure 8 or a carboxy-terminal truncation of Pro^{123}-Thr^{179} of Figure 8.

4. The tumor necrosis binding protein according to any one of Claims 1 through 3, wherein said amino acid sequence is nonglycosylated.

5. The tumor necrosis binding protein according to any one of Claims 1 through 3, wherein said amino acid sequence is glycosylated.

6. The tumor necrosis binding protein according to any one of Claims 1 through 5, wherein the protein is conjugated to a water soluble polymer.

7. A polyvalent tumor necrosis binding protein comprising at least one tumor necrosis binding protein according to any one of Claims 1 though 6.

8. A polyvalent tumor necrosis binding protein having the formula R_1-X-R_2, wherein:

X comprises a linker, wherein said linker is a water soluble polymer; and

R_1 and R_2 are biologically-active molecules covalently bonded to said water soluble polymer, wherein at least one of R_1 and R_2 is a tumor necrosis binding protein according to any one of Claims 1 though 6.

9. The polyvalent tumor necrosis binding protein of Claim 8, wherein the water soluble polymer is polyethylene glycol.

10. The polyvalent tumor necrosis binding protein of Claim 9, wherein the protein is selected from the group consisting of sTNFR-I 2.6D/C105db and sTNFR-I 2.6D/C106db.

11. The tumor necrosis binding protein according to any one of Claims 1 through 10 for use in treating TNF-mediated disease.

12. The tumor necrosis binding protein according to any one of Claims 1 through 10 for use in treating arthritis.

13. A polynucleotide encoding the tumor necrosis binding protein according to any one of Claims 1 through 3.

14. A nucleic acid sequence comprising a tumor necrosis factor binding protein encoded by a nucleotide sequence selected from the following:

(a) a cDNA sequence as shown in Fig. 2;
(b) a cDNA sequence as shown in Fig. 3;
(c) a cDNA sequence as shown in Fig. 4;
(d) a cDNA sequence as shown in Fig. 5;
(e) a cDNA sequence as shown in Fig. 6;
(f) a cDNA sequence as shown in Fig. 7;
(g) a sequence which is degenerate in the coding regions or portions thereof of (a), (b), (c), (d), (e) and (f);
(h) a sequence which hybridizes to (a), (b), (c), (d), (e), (f) and (g); and
(i) a sequence which is complementary to (a), (b), (c), (d), (e), (f), (g) and (h),

provided however, that the nucleic acid does not encode a protein having the formula

R_1-[Cys^{19}-Cys^{103}]-FCCSLCL-R_3

wherein [Cys^{19}-Cys^{103}] represents residues 19 through 103 of sTNFR-I, the amino acid residue numbering scheme of which is provided in Figure 1 (SEQ ID NO:2) to facilitate the comparison;
wherein R_1 represents a methionylated or nonmethionylated amine group of an amino acid sequence comprising NNSIC and R_3 represents a carboxyl group of amino acid residues Asn^{111}-Asn^{161} of Figure 1 or a carboxy-terminal truncation of Asn^{111}-Asn^{161} of Figure 1.

15. A polynucleotide having the sequence as set forth in Figures 2, 3, 4, 5, 6, or 7, or a portion thereof.

16. A vector comprising a polynucleotide of any one of Claims 13 through 15 operatively linked to an expression control sequence.

17. A prokaryotic or eukaryotic host cell containing a polynucleotide of any one of Claims 13 through 15.

18. A method comprising growing host cells of Claim 17 in a suitable nutrient medium and, optionally, isolating said truncated sTNFR from said cells or said nutrient medium.

19. The method for producing the tumor necrosis binding protein according to Claim 18, wherein said host cells are *E. coli*.

20. The method for producing the tumor necrosis factor binding protein according to Claim 18, wherein said host cells are Chinese hamster ovary cells.

21. A method comprising the steps of:

(a) culturing a prokaryotic or eukaryotic host cell of Claim 17;

(b) maintaining said host cell under conditions allowing the expression of truncated sTNFR by said host cell; and

(c) optionally isolating the truncated sTNFR expressed by said host cell.

22. A tumor necrosis binding protein which is the recombinant expression product of a prokaryotic or eukaryotic host cell containing an exogenous polynucleotide of any one of Claims 13 through 15.

23. A pharmaceutical composition comprising the tumor necrosis factor binding protein according to any one of Claims 1 through 10 in association with a pharmaceutically acceptable vehicle.

24. A pharmaceutical composition comprising the tumor necrosis factor binding protein produced in accordance with the method of Claim 18 in association with a pharmaceutically acceptable vehicle.

25. A pharmaceutical composition comprising the tumor necrosis factor binding protein produced in accordance with the method of Claim 21 in association with a pharmaceutically acceptable vehicle.

26. A method of treating a TNF-mediated disease comprising administering to a patient the pharmaceutical composition of Claims 23 through 25.

27. The method of claim 26, wherein the TNF-mediated disease is arthritis.

28. A method of preparing a pharmaceutical composition wherein a therapeutically effective amount of the tumor necrosis factor binding protein according to any one of Claims 1 though 10 is mixed with one or more pharmaceutically acceptable vehicles.

29. The use of the tumor necrosis factor binding protein according to any one of Claims 1 though 10 for treating a TNF-mediated disease.

30. The use of the tumor necrosis factor binding protein according to Claim 29 for treating arthritis.

31. A kit for preparing an aqueous protein formulation comprising the tumor necrosis factor binding protein according to any one of Claims 1 through 10 and a second container having a physiologically acceptable solvent.